A STUDY OF

THYROID PROFILE IN CHRONIC KIDNEY

DISEASE

DISSERTATION SUBMITTED FOR M.D.DEGREE

EXAMINATION

BRANCH I – GENERAL MEDICINE

APRIL 2011

TIRUNELVELI MEDICAL COLLEGE

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

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CERTIFICATE

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ACKNOWLEDGEMENT

I am extremely thankful to our beloved ***Dean***, **Dr.N.Palaniappan.M.D**., for granting me permission to carry out this study in Tirunelveli medical college hospital.

It is an immense pleasure to acknowledge **Dr.J.Kaniraj Peter.M.D.,** ***Professor and Head of the department, Department of medicine,*** who has given the moral support, philosophical guidance and ever available help to carry out this study.

With deepest appreciation and gratitude I thank **Dr.R.Geetha Rani M.D.,** my unit chief and Associate Professor of medicine and **Dr.V.Ramasubramanian, M.D., D.M.,** Professor and Head of Nephrology, Tirunelveli Medical College, my guide and mentor to carry out this study.

I thank Professor and the staff belonging to the department of biochemistry and radiology.

I also thank **Dr.S.S.Nazar M.D.,** and **Dr.M.Mohamed Rafi M.D.,** ***assistant professors*** for their moral support.

Finally with Almighty God and with the cooperation of the patients, I completed this study.

ABBREVIATIONS

CKD	-	Chronic Kidney Disease
CRF	-	Chronic Renal Failure
ESRD	-	End stage renal disease
FT4	-	Free Thyroxine
GFR	-	Glomerular Filtration Rate
PTH	-	Parathyroid hormone
T3	-	Triiodothyronine
T4	-	Thyroxine
TRH	-	Thyrotropin Releasing Hormone
TSH	-	Thyroid Stimulating Hormone
TBG	-	Thyroxine Binding Globulin
HD	-	Hemodialysis
PD	-	Peritoneal Dialysis
TTR	-	Transthyretin
SES	-	Sick Euthyroid Syndrome
TH	-	Thyroid Hormone
NS	-	Nephrotic Syndrome
rh EPO	-	recombinant human Erythropoietin

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INTRODUCTION

Patients with chronic renal failure often have signs & symptoms suggestive of thyroid dysfunction. These findings include dry skin, sallow complexion, low temperature, cold intolerance, decreased basal metabolic rate, lethargy, fatigue, edema & hyporeflexia. Various studies of thyroid functions in uremic patients have been carried out which have shown conflicting results. Hyperthyroidism, hypothyroidism & euthyroid state have all been reported by various workers.

Serum triiodothyronine (T3) levels were consistently found to be low without any regard to treatment of CRF. Serum total & free thyroxine (T4) concentrations have been reported as low, normal or high. Serum thyroid stimulating hormone (TSH) levels were found to be normal in most patients of CRF even in those whose CRF is complicated by low T3 concentration.

A reduction in total T3, but not in free T3 concentrations was associated with an increased all-cause and cardiovascular mortality in euthyroid CKD patients[45]. Total and free T3 behave as survival markers in patients with CKD both in HD and in PD.

Prevalence of hypothyroidism in end stage renal disease (ESRD) have been estimated between 0 and 9%. There is also increased prevalence of goiter in patients with ESRD. Though there are multiple factors which predicts the overall mortality and severity of renal disease, one among the important factor is thyroid dysfunction. So it is prudent for the internist and

treating physician to be aware of thyroid dysfunction so that early intervention can be instituted to improve the outcome. In view of variability of thyroid function test in patients with CRF in previous studies, a cross-sectional study on thyroid function in CRF patient in Department of Medicine, TIRUNELVELI Medical College Hospital, has been undertaken.

AIM OF THE STUDY

1. To study the prevalence of thyroid dysfunction in patients with chronic renal failure.

2. To study the correlation between thyroid dysfunction and severity of renal failure.

3. To differentiate primary thyroid diseases from thyroid dysfunction due to chronic renal failure.

REVIEW OF LITERATURE

Chronic kidney disease (CKD)[1] encompasses a spectrum of different pathophysiologic processes associated with abnormal kidney function, and a progressive decline in glomerular filtration rate (GFR).

DEFINITION CRITERIA:

Chronic Kidney Disease is defined according to the presence or absence of markers of kidney damage and the level of kidney function (GFR), irrespective of kidney disease (the specific diagnosis).

1. Kidney damage for ≥3months,as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by either,

a) Pathological abnormalities or

b) Markers of kidney damage, including abnormalities in the composition of the blood or urine or abnormalities in imaging tests.

CLASSIFICATION:

A widely accepted classification, based on recent guidelines of the National Kidney Foundation [Kidney Dialysis Outcomes Quality Initiative (KDOQI)][2], in which stages of CKD are defined according to the estimated GFR.

Stage	GFR ml/min/1.73m^2
0	>90[a]
1	>90[b]
2	60-89
3	30-59
4	15-29
5	<15

a. with risk factors for CKD
b. with demonstrated kidney damage (persistent protienuria, abnormal urine sediment, abnormal blood and urine chemistry, abnormal imaging studies)

PATHOPHYSIOLOGY:

The pathophysiology of CKD involves two broad sets of mechanisms of damage:

1. Initiating mechanisms specific to the underlying etiology (e.g: immune complexes and mediators of inflammation in certain types of

glomerulonephritis or toxin exposure in certain diseases of the renal tubules and interstitium),

2. Set of progressive mechanisms, involving hyperfiltration and hypertrophy of the remaining viable nephrons, that are a common consequence following long-term reduction of renal mass, irrespective of underlying etiology. The responses to reduction in nephron number are mediated by vasoactive hormones, cytokines, and growth factors. Eventually, these short-term adaptations of hypertrophy and hyperfiltration become maladaptive as the increased pressure and flow predisposes to sclerosis and dropout of the remaining nephrons.

UREMIA:

Hundreds of toxins that accumulate in renal failure have been implicated in the uremic syndrome. These include water-soluble, hydrophobic, protein-bound, charged and uncharged compounds. Additional categories of nitrogenous excretory products include guanido compounds, urates and hippurates, products of nucleic acid metabolism, polyamines, myoinositol, phenols, benzoates, and indoles. Compounds with a molecular mass between 500 and 1500 Da, the so-called middle molecules, are also retained and contribute to morbidity and mortality. The pathophysiology of the uremic syndrome can be divided into manifestations in three spheres of dysfunction: (1) those consequent to the accumulation of toxins normally undergoing renal excretion, including products of protein metabolism

(2) those consequent to the loss of other renal functions, such as fluid and electrolyte homeostasis and hormone regulation and (3) progressive systemic inflammation and its vascular and nutritional consequences.

MANIFESTATIONS OF CHRONIC KIDNEY DISEASE

Stages 1 and 2 CKD are usually not associated with any symptoms arising from the decrement in GFR. However, there may be symptoms from the underlying renal disease itself, such as edema in patients with nephrotic syndrome or signs of hypertension secondary to the renal parenchymal disease in patients with polycystic kidney disease, some forms of glomerulonephritis and many other parenchymal and vascular renal diseases, even with well-preserved GFR. If the decline in GFR progresses to stages 3 and 4, clinical and laboratory complications of CKD become more prominent. Virtually all organ systems are affected, but the most evident complications include anemia and associated easy fatiguability, decreasing appetite with progressive malnutrition, abnormalities in calcium, phosphorus and mineral-regulating hormones, such as $1,25(OH)_2D_3$ (calcitriol) and parathyroid hormone (PTH) and abnormalities in sodium, potassium, water and acid-base homeostasis. If the patient progresses to stage 5 CKD, toxins accumulate such that patients usually experience a marked disturbance in their activities of daily living, well-being, nutritional status and water and electrolyte homeostasis, eventuating in the **uremic syndrome**

PHYSIOLOGY OF THYROID HORMONES:

The thyroid gland produces two related hormones, thyroxine (T4) and triiodothyronine (T3). Acting through nuclear receptors, these hormones play a critical role in cell differentiation during development and help to maintain thermogenic and metabolic homeostasis in the adult. Autoimmune disorders of the thyroid gland can either stimulate the overproduction of thyroid hormones (thyrotoxicosis) or cause glandular destruction and hormone deficiency (hypothyroidism).

Iodide uptake is a critical first step in thyroid hormone synthesis. Ingested iodine is bound to serum proteins, particularly albumin. Unbound iodine is excreted in the urine. The thyroid gland extracts iodine from the circulation in a highly efficient manner.

ORGANIFICATION, COUPLING, STORAGE AND RELEASE

After iodide enters the thyroid, it is trapped and transported to the apical membrane of thyroid follicular cells, where it is oxidized in an organification reaction that involves TPO and hydrogen peroxide. The iodotyrosines in Tg are then coupled via an ether linkage in a reaction that is also catalyzed by TPO. Either T4 or T3 can be produced by this reaction, depending on the number of iodine atoms present in the iodotyrosines. After coupling, Tg is taken back into the thyroid cell, where it is processed in lysosomes to release T4 and T3. Uncoupled mono- and diiodotyrosines are

deiodinated by the enzyme dehalogenase, thereby recycling any iodide that is not converted into thyroid hormones.

REGULATION OF THYROID AXIS

TSH, secreted by the thyrotrope cells of the anterior pituitary, plays a pivotal role in control of the thyroid axis and serves as the most useful physiologic marker of thyroid hormone action.

Hypothalamic TRH stimulates pituitary production of TSH, which in turn, stimulates thyroid hormone synthesis and secretion. Thyroid hormones feed back to inhibit TRH and TSH production. The "set-point" in this axis is established by TSH. TRH is the major positive regulator of TSH synthesis and secretion. Peak TSH secretion occurs ~15 min after administration of exogenous TRH. Dopamine, glucocorticoids and somatostatin suppress TSH but are not of major physiologic importance except when these agents are administered in pharmacologic doses.

TSH is released in a pulsatile manner and exhibits a diurnal rhythm, its highest levels occur at night. TSH has a relatively long plasma half-life (50 min).

FACTORS INFLUENCE THYROID HORMONE SYNTHESIS AND RELEASE:

Although TSH is the dominant hormonal regulator of thyroid gland growth and function, a variety of growth factors, most produced locally in the thyroid gland, also influence thyroid hormone synthesis.

These include insulin-like growth factor I (IGF-I), epidermal growth factor, transforming growth factor (TGF), endothelins, and various cytokines. Excess iodide transiently inhibits thyroid iodide organification, a phenomenon known as the Wolff-Chaikoff effect. In individuals with a normal thyroid, the gland escapes from this inhibitory effect and iodide organification resumes. The suppressive action of high iodide may persist, in patients with underlying autoimmune thyroid disease.

CHARACTERISTICS OF CIRCULATING T4 AND T3

Hormone Property	**T4**	**T3**
Serum concentrations		
Total hormone	8ug/dL	0.14 ug/dL
Fraction of total hormone in the free form	0.02%	0.3%
Free (unbound) hormone	21 x 10^{-12} *M*	6 x 10^{-12} *M*
Serum half-life	7 d	0.75 d
Fraction directly from the thyroid	100%	20%
Production rate, including peripheral conversion	90 ug/d	32 ug/d
Intracellular hormone fraction	20%	70%
Relative metabolic potency	0.3	1
Receptor binding	10^{-10} *M*	10^{-11} *M*

ABNORMALITIES OF THYROID HORMONE BINDING PROTEINS:

Mutations in TBG, TTR and albumin may increase the binding affinity for T4 and/or T3 and cause disorders known as euthyroid hyperthyroxinemia or familial dysalbuminemic hyperthyroxinemia (FDH). These disorders result in increased total T4 and/or T3, but unbound hormone levels are normal.

Certain medications, such as salicylates and salsalate, can displace thyroid hormones from circulating binding proteins. Although these drugs transiently perturb the thyroid axis by increasing free thyroid hormone levels, TSH is suppressed until a new steady state is reached, thereby restoring euthyroidism. Circulating factors associated with acute illness may also displace thyroid hormone from binding proteins.

DEIODINASES:

T4 may be thought of as a precursor for the more potent T3. T4 is converted to T3 by the deiodinase enzymes. Type I deiodinase, which is located primarily in thyroid, liver and kidney, has a relatively low affinity for T4. Type II deiodinase has a higher affinity for T4 and is found primarily in the pituitary gland, brain, brown fat, and thyroid gland. Type II deiodinase is also regulated by thyroid hormone. Hypothyroidism induces the enzyme, resulting in enhanced T4 to T3 conversion in tissues such as brain and pituitary. T4 to T3 conversion is impaired by fasting, systemic illness or

acute trauma, oral contrast agents and a variety of medications (propylthiouracil, propranolol, amiodarone, glucocorticoids). Type III deiodinase inactivates T4 and T3 and is the most important source of reverse T3 (rT3).

HYPOTHYROIDISM:

Hypothyroidism is a clinical syndrome caused by decreased level of thyroid hormones. It can be **primary** in which there is intrinsic disorder of thyroid gland or it may be **secondary** in which there is pituitary or hypothalamic defect.

Florid hypothyroidism can be diagnosed clinically. The **symptoms** of hypothyroidism in descending order of frequency are:

- Tiredness, weakness
- Dry Skin
- Feeling Cold
- Hair Loss
- Difficulty in concentrating and poor memory
- Constipation
- Weight gain with poor appetite
- Dyspnea
- Hoarse voice
- Menorrhagia (Later amenorrhea)
- Paraesthesia
- Impaired hearing

The signs of hypothyroidism in descending order of frequency are as follows:

- Dry coarse skin
- Cool peripheral extremities
- Puffy face, hands and feet (myxedema)
- Diffuse alopecia
- Bradycardia
- Peripheral edema
- Delayed tendon reflex relaxation
- Carpal tunnel syndrome
- Serous cavity effusions

In biochemical studies, TSH is the single most important parameter for screening hypothyroidism. A normal TSH level rules out primary hypothyroidism, but not secondary. To diagnose primary hypothyroidism, TSH level should be above 20 μIU/ml or at least above 10 μIU/ml if clinical features strongly suggest.

In the presence of elevated TSH, low T4 especially free T4 is necessary to confirm hypothyroidism. Circulating free T3 is usually reduced. But it may be normal in 25% of hypothyroid patients. So, T3 measurements are not reliable indicators of hypothyroidism.

HYPERTHYROIDISM:

Hyperthyroidism is a clinical syndrome which results from exposure of the body tissues to excess circulating levels of free thyroid hormones.

The symptoms of hyperthyroidism in descending order of frequency are as follows:

- Hyper activity, irritability, dysphonia
- Heat intolerance and sweating
- Palpitations
- Fatigue and weakness
- Weight Loss with increased appetite
- Diarrhoea
- Polyuria
- Oligomenorrhea, loss of libido

The signs of hyperthyroidism in descending order of frequency are as follows:

- Tachycardia; atrial fibrillation in elderly
- Tremor
- Goiter
- Warm, moist skin
- Muscle weakness, proximal myopathy
- Lid retraction or lag
- Gynaecomastia

Laboratory investigation shows TSH below normal level. Free and total thyroid hormone levels are increased.

In 2 to 5% of patients, only T3 is increased, a condition called T3 thyrotoxicosis**.** Occasionally, total and free T4 will be increased with normal T3 level. This condition is called T4 thyrotoxicosis.

SICK EUTHYROID SYNDROME:

Any acute, severe illness can cause abnormalities of circulating TSH or thyroid hormone levels in the absence of underlying thyroid disease, making these measurements potentially misleading. The major cause of these hormonal changes is the release of cytokines such as IL-6. Unless a thyroid disorder is strongly suspected, the routine testing of thyroid function should be avoided in acutely ill patients.

The most common hormone pattern in **sick euthyroid syndrome (SES)** is a decrease in total and unbound T3 levels (low T3 syndrome) with normal levels of T4 and TSH. The magnitude of the fall in T3 correlates with the severity of the illness. T4 conversion to T3 via peripheral deiodination is impaired, leading to increased reverse T3 (rT3). Despite this effect, decreased clearance rather than increased production is the major basis for increased rT3.

Very sick patients may exhibit a dramatic fall in total T4 and T3 levels (low T4 syndrome). This state has a poor prognosis. A key factor in the fall in T4 levels is altered binding to TBG. T4 assays usually demonstrate a

normal unbound T4 level in such patients, depending on the assay method used. Fluctuation in TSH levels also creates challenges in the interpretation of thyroid function in sick patients, levels may range from <0.1 to >20 mU/L. The exact mechanisms underlying the subnormal TSH seen in 10% of sick patients and the increased TSH seen in 5% remain unclear but may be mediated by cytokines including IL-12 and IL-18.

Any severe illness can induce changes in thyroid hormone levels, but certain disorders exhibit a distinctive pattern of abnormalities. Acute liver disease is associated with an initial rise in total (but not unbound) T3 and T4 levels, due to TBG release. The levels become subnormal with progression to liver failure. A transient increase in total and unbound T4 levels, usually with a normal T3 level, is seen in 5–30% of acutely ill psychiatric patients. TSH values may be transiently low, normal or high in these patients. In the early stage of HIV infection, T3 and T4 levels rise, even if there is weight loss. T3 levels fall with progression to AIDS (Acquired immune Deficiency Syndrome), but TSH usually remains normal. Renal disease is often accompanied by low T3 concentrations, but with normal rather than increased rT3 levels, due to an unknown factor that increases uptake of rT3 into the liver.

Treatment of SES with thyroid hormone (T4 and/or T3) is controversial, but most authorities recommend monitoring the patient's thyroid function tests during recovery without administering thyroid

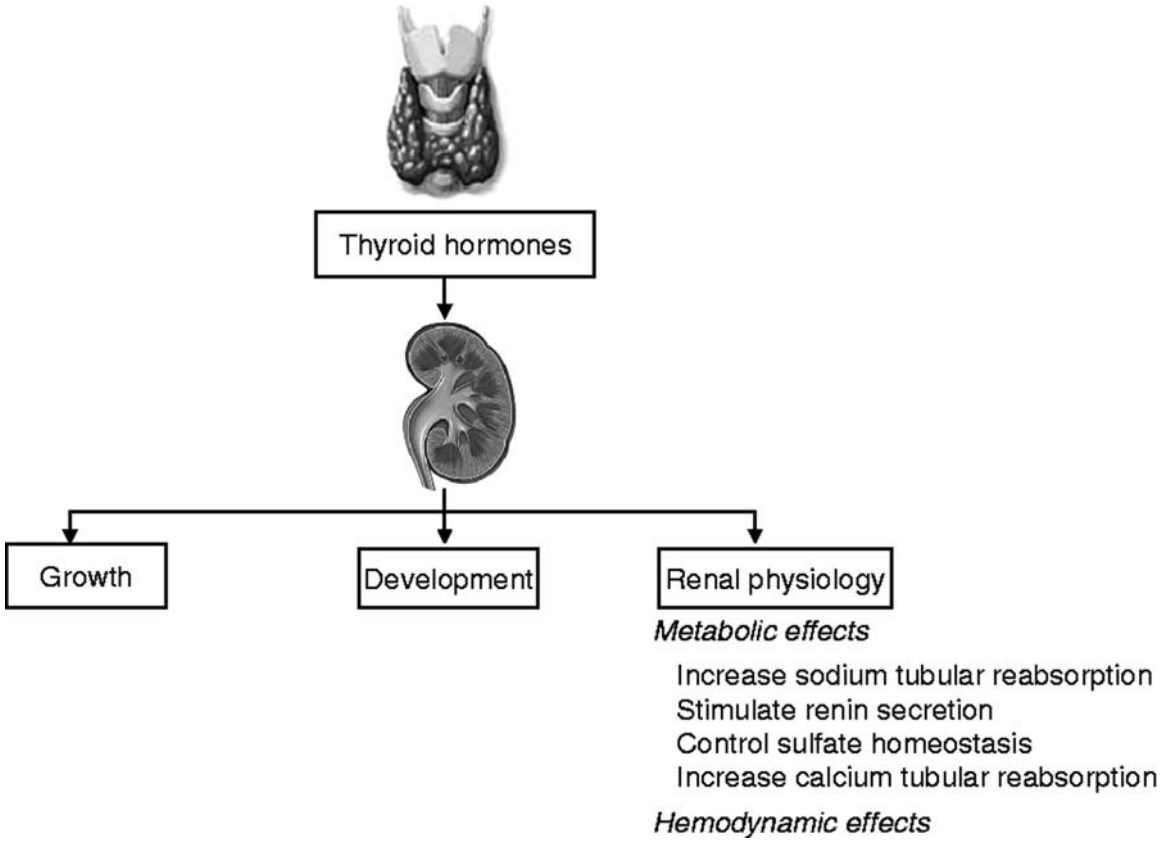
hormone, unless there is historic or clinical evidence suggestive of hypothyroidism.

RELATION BETWEEN THYROID HORMONES AND KIDNEY:

Thyroid hormones (TH) are necessary for growth and development of the kidney and for the maintenance of water and electrolyte homeostasis. On the other hand, kidney is involved in the metabolism and elimination of Thyroid Hormone. From a clinical practice viewpoint, it should be mentioned that both hypothyroidism and hyperthyroidism are accompanied by remarkable alterations in the metabolism of water and electrolyte, as well as in cardiovascular function. All these effects generate changes in water and electrolyte kidney management [11]. Moreover, the decline of kidney function is accompanied by changes in the synthesis, secretion, metabolism and elimination of Thyroid Hormone. Thyroid dysfunction acquires special characteristics in those patients with advanced kidney disease.

EFFECT OF THYROID HORMONES ON RENAL PHYSIOLOGY:

Thyroid Hormone plays an important role in growth, development and physiology of the kidney[12]. It is known that hypothyroidism reduces and hyperthyroidism increases the kidney-to-body weight ratio by a not fully understood mechanism [13].



Thyroid Hormone have a hold upon tubular transport of sodium, via their actions on the sodium–potassium ATP pump (Na^+/K^+ ATPase) and on the potassium permeability in the membrane of proximal tubules [14, 15, 16]. As it occurs with Na^+, the reduction of TH activity at kidney level is accompanied by a decrease in the absorption of calcium at tubular level without affecting magnesium[18]. Thyroid Hormone stimulates renin release by the juxtaglomerular cells through a mechanism independent of the ouabain-sensitive sodium pump and protein synthesis[19] and influence kidney angiotensinase activity [20].

EFFECTS OF THRYOID DYSFUNCTION ON THE KIDNEY:

Thyroid dysfunction causes significant changes in kidney function. Both hypothyroidism and hyperthyroidism affect renal blood flow, GFR, tubular function, electrolytes homeostasis, electrolyte pump functions and kidney structure[21].

Hypothyroidism	**Thyrotoxicosis**
Increased serum creatinine	Decreased serum creatinine
Decreased glomerular filtration	Increased glomerular filtration
Decreased renal plasma flow	Increased renal plasma flow
Decreased sodium reabsorption	Increased tubular reabsorption
Decreased renal ability to dilute urine	Resistance to rhEPO action?
Hyponatremia	

KIDNEY DISEASE ASSOCIATED WITH THYROID DYSFUNCTION:

Different types of kidney diseases can be associated with various disorders of thyroid function [22].

Glomerular disease:

Thyroid disease may be linked to different forms of glomerulonephritis [23]. Both hypothyroidism and hyperthyroidism can coincide with different forms of glomerular disease. The more frequent form is membranous glomerulopathy associated with nephrotic syndrome (NS) [24].

Thyroid dysfunction has been reported to be associated with IgA glomerulonephritis[25], mesangiocapillary or membranoproliferative glomerulonephritis and minimal change glomerulonephritis .

Several mechanisms have been involved in these associations. Proteinuria may promote the development of primary hypothyroidism and the immune activation of the thyroid or kidney disorders could induce the formation of immune complexes [26]. The presence of immune complexes is common in patients with thyroid disease. 33–55% patients with an autoimmune process have correlation with the presence of thyroid peroxidase antibodies, but not with the titre of these antibodies[27]. Several data support the autoimmune pathogenesis for the association: i) the association of kidney and thyroid diseases of autoimmune origin, ii) its association with other autoimmune diseases such as type 1 diabetes and iii) the presence of deposits of immunoglobulins and thyroglobulin in the glomeruli of some patients[28] . Although autoimmune thyroid disease has occasionally been reported in patients with glomerulonephritis, no causal relationship between the two disorders has been proved so far. Glomerular disease in general is associated and occasionally caused by autoimmune disease (e.g. lupus nephritis, antineutrophil cytoplasmic antibodies (ANCA) associated vasculitis) that can be associated to autoimmune thyroid disease.

Tubular disease

Although less frequent than glomerular disease, tubular or tubulointerstitial damage has also been reported to be associated with thyroid dysfunction [29]. Isolated cases of hyperthyroidism have been reported in association with tubulointerstitial nephritis and uveitis, a self-limited syndrome of unknown etiology that responds to glucocorticoids[30]. In these cases, the etiology of hyperthyroidism was not Grave's disease, but rather a destructive thyroiditis with the absence of thyroid autoimmunity, low uptake in thyroid scintigraphy, and adequate response to steroid therapy. Tubulointerstitial nephritis and hyperthyroidism has been reported to be associated in patients under treatment with rifampicin [31].

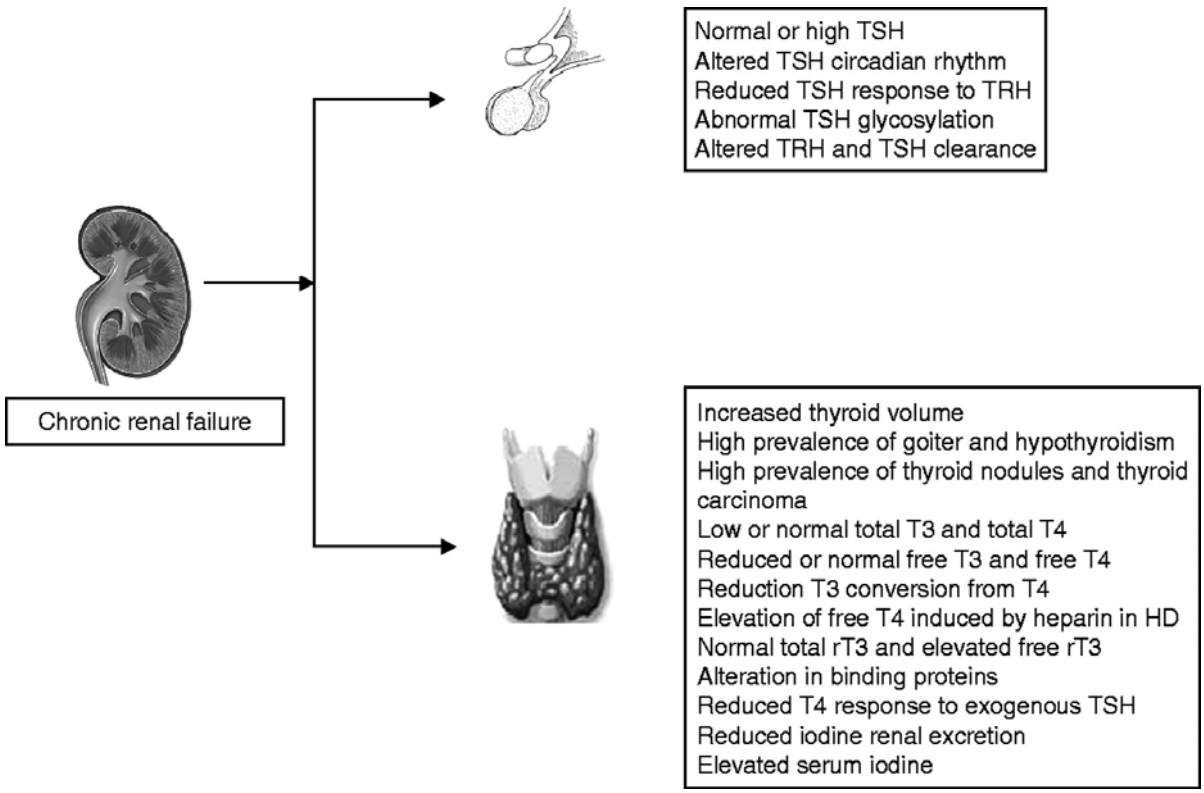
Nephrotic syndrome

Nephrotic Syndrome is associated with changes in serum Thyroid Hormone levels[32]. Urinary losses of binding proteins such as thyroxine binding globulin (TBG), transthyretin or pre-albumin, albumin and Thyroid Hormone bound to them, result in a reduction in serum total thyroxine (T4) and sometimes, in total T3 levels. These hormonal changes are related both to the degree of proteinuria and to serum albumin levels [33]. However, patients often remain euthyroid, because free T4 and T3 levels are usually normal. This suggests that thyroid is able to compensate for hormonal urinary losses keeping the patient euthyroid. However, in patients with low thyroid reserve overt hypothyroidism can develop. Similarly, Nephrotic

Syndrome may increase the exogenous levothyroxine needs in patients with hypothyroidism.

CHRONIC KIDNEY DISEASE:

CKD affects both hypothalamus–pituitary–thyroid axis and TH peripheral metabolism. Uremia influences the function and size of the thyroid. Uremic patients have an increased thyroid volume compared with subjects with normal renal function and a higher prevalence of goiter, mainly in women[36]. Also, thyroid nodules and thyroid carcinoma are more common in uremic patients than in the general population.



Serum TSH concentrations are usually normal or elevated in CKD, but its response to its releasing hormone (TRH) is generally low. These findings suggest the presence of intrathyroidal and pituitary disturbances associated with uremia [37]. Also, both TSH circadian rhythm and TSH glycosylation are altered in CKD. The latter may compromise TSH bioactivity.

Free and total T3 and T4 concentrations are usually normal or low in patients with CKD. The reduction in T3 levels (low T3 syndrome) is the most frequently observed thyroid alteration in these patients. The reduction in T3 concentrations has been linked to a decrease in the peripheral synthesis of T3 from T4. Chronic metabolic acidosis associated with the CKD may contribute in this effect [38]. Although free and total T4 concentrations may be normal or slightly reduced, sometimes free T4 may be high due to the effect of heparin used in anticoagulation during hemodialysis (HD), which inhibits T4 binding to its binding proteins.

In CKD patients, the sick euthyroid state is characterized by the absence of total rT3 rising, a typical feature in other patients with non-thyroidal disease[39]. Despite the fact that the total rT3 clearance in CKD patients is diminished, there is a redistribution of rT3 from the vascular to the extra vascular space and an increase in rT3 cellular uptake. However, free rT3 concentrations are high due to a reduction in its renal clearance.

CKD is associated with a higher prevalence of primary hypothyroidism, both overt and subclinical, but not with hyperthyroidism.

In fact, the prevalence of primary hypothyroidism, mainly in the subclinical form, increases as GFR decreases [40]. A recent study has shown a prevalence of subclinical hypothyroidism of 7% in patients with estimated GFR ≥90 ml/min per 1.73 m^2 that increased to 17.9% in subjects with GFR <60 ml/min per 1.73 m^2. The prevalence of hypothyroidism is higher in women and is associated with an increased frequency of high titers of anti-thyroid antibodies.

The prevalence of hyperthyroidism in CKD is similar to that found in general population (~1%), in areas with inadequate intake of iodine. On the other hand, uremic patients undergoing dialysis with hyperthyroidism due to either Grave's disease or toxic multinodular goiter can be adequately treated with therapeutic doses of $\mathbf{I}^{131}$. Moreover, hyperthyroidism has been considered as one of the many causes of anemia resistant to recombinant human erythropoietin (rh-EPO) in CKD patients on HD with an adequate response to antithyroid treatment.

The kidney contributes to the iodine clearance primarily through glomerular filtration. Serum iodine concentrations are high in CKD but are not correlated with the degree of kidney failure. This iodine excess has been linked to increased prevalence of goiter and hypothyroidism reported in CKD. A high exposure to iodine facilitates the development of hypothyroidism in CKD patients. Some authors have reported that a restriction of dietary iodine in uremic patients on HD can correct

the hypothyroidism avoiding the need for hormone replacement with levothyroxine [41].

EFFECTS OF DIALYSIS ON THYROID FUNCTION:

Hemodialysis

Most HD patients are euthyroid. Hypothyroidism is not infrequent in these patients. However, a diagnosis of hypothyroidism in HD patients should not be made solely on the basis of reduced T4 and T3 levels but requires documentation of substantial TSH elevation (TSH>5 mIU/l but <20 mIU/l may occur in 20% of uremic patients and are more indicative of non-thyroidal illness than hypothyroidism). HD is associated with alterations in the concentration of circulating Thyroid Hormone, usually to a reduction in serum total and free T3 concentrations. This reduction is associated with systemic acidosis, time on dialysis, and some markers of endothelial damage and inflammation. Low Thyroid Hormone may be a protective adaptation for nitrogen conservation and therefore inappropriate Thyroid Hormone supplementation can result in excessive protein nitrogen wasting in these patients. HD influences the cellular transport of Thyroid Hormone. This effect could act as a compensatory mechanism to neutralize the thyroid dysfunction in order to maintain euthyroid status [42].

Treatment with ablative dose of $\mathbf{I^{131}}$ has been successfully used in the treatment of differentiated thyroid carcinoma in patients on HD

Peritoneal dialysis:

The most common thyroid dysfunction in peritoneal dialysis (PD) patients is primary hypothyroidism, especially subclinical hypothyroidism (27.5%) [43]. This entity might be implicated in cardiac dysfunction in PD patients due to the fact that these patients show lower left ventricular ejection fractions and fractional shortening at endocardial levels compared with those with normal TSH levels. Other common alteration in thyroid function tests is low T3 syndrome (16%). The high protein loss induced by this type of dialysis could be related to an increased incidence of thyroid dysfunction. One of the important issues in PD patients is the continuous loss (due to the continuous nature of the method) of substantial amounts of proteins in the peritoneal cavity. Nevertheless, TBG concentrations remain within normal limits in these patients. When hypothyroidism develops, left ventricular function can be compromised but this is not specific to PD patients.

Thyroid function and renal transplantation

Kidney transplantation is associated with abnormalities in thyroid function, mainly a reduction in T3 concentrations. An independent relationship between T3 with different markers of endothelial dysfunction has been reported. Both thyroid volume and serum concentration of free T3 are correlated with the graft function. A positive correlation between serum creatinine and thyroid volume has been found. Patients with

diminished values of T3 before transplantation are at increased risk of graft failure, thus suggesting that T3 quantification might be a potential marker for this risk. However, treatment with T3 does not appear to prolong the half-life and function of the graft [44].

MANAGEMENT

Several studies have been conducted in patients with the T3 syndrome in order to correct the thyroid profile by treating with Levothyroxine and Triiodothyronine.

Gregory Brent et al.[47] conducted study in non-thyroidal illness patients by treating all the patients with serum total T4 less than 5 μg/dl with 1.5 μg/Kg of Levothyroxine for 2 weeks. Thyroxine level increased significantly in treated patients. Serum T3 levels were also raised. But mortality was increased in treatment group on day 5 – 17.

Carter et al.[48] studied effects of Triiodothyronine administration in patients with chronic renal failure. Study showed serum T3 level did not change over a period of 12 weeks. But the mean serum T4 and TSH levels were affected significantly. There was no subjective improvement in these patients.

Based on this observation, it has been suggested that low serum T3 level in patients with severe renal failure is metabolically protective and it is interpreted as physiological adaptation to reduce basal metabolic rate (BMR)

and to conserve energy in an adverse environment. Hence, this condition has been renamed as **"Thyroid hormone adaptation syndrome"**

Administration of T4 or T3 causes suppression of TSH and increases the catabolism. So, administration of thyroid hormone is not beneficial. Study also showed increased morality with the treatment. Therefore, thyroid hormone should not be given in CRF unless true hypothyroidism can be documented.

Thyroid function, morbidity, and mortality in kidney disease

There is a relationship between plasma levels of T3 and various markers of inflammation, nutrition, and endothelial activation in patients with CKD [45]. These patients show an association between low serum values of T3 with inflammation markers (elevated levels of high sensitivity C-reactive protein, interleukin 6(IL-6) and vascular adhesion molecule-1) and nutrition (decrease of albumin and IGF-1), and cardiac function. The lower the concentration of T3, the greater the degree of inflammation and poorer the nutritional status and cardiac function. Therefore, low T3 is associated with a survival disadvantage. The relationship between survival and T4 is less defined.

A reduction in total T3, but not in free T3 concentrations was associated with an increased all-cause and cardiovascular mortality in euthyroid CKD patients. Total and free T3 behave as survival markers in patients with CKD both in HD and in PD. For these reasons, some authors

have recommended measuring T3 levels to assess the relationship between thyroid dysfunction and risk of mortality in this population. Finally, it has been recently reported that low levels of T3 before renal transplantation are associated with decreased survival of the graft.

Several factors, including malnutrition and intercurrent processes, may be involved in the reduction of serum T3 in uremic patients. Fasting and disease alter iodothyronine deiodination, thus reducing peripheral production of T3. The presence of chronic protein malnutrition is associated with a reduction of binding protein synthesis and could reduce plasma total T3 concentration. TNF-α and interleukin-1 inhibit the expression of type 1 5'-deiodinase, the enzyme responsible for T4 to T3 conversion in peripheral tissues. This would explain how chronic inflammation and vascular damage associated to CKD, interfere with the normal process of T3 synthesis from T4 [46].

SUMMARY:

Kidney and thyroid function and dysfunction are interrelated through several mechanisms. From a clinical perspective, in patients with kidney disease, it is generally sufficient to use thyroid function tests commonly used in the clinic. However, to avoid mistakes in diagnosis, it is important to know the effects of hypothyroidism and hyperthyroidism on renal function, as well as the changes in thyroid function tests induced by chronic kidney disease. Drugs used in the treatment of thyroid and

kidney diseases may induce changes in renal and thyroid physiology respectively. Treatment of CKD by HD, PD or renal transplantation is also accompanied by specific changes in thyroid physiology. In patients with differentiated thyroid carcinoma, some modifications in the usual therapies may be necessary, especially in the dose of $\mathbf{I^{131}}$, in the presence of a decline in renal function. On the other hand, recent investigations have shown interesting relationships in neoplastic diseases affecting the thyroid and the kidney. A relationship between T3 levels and mortality has been proven in uremic patients. The relationship between TSH and survival, well established in other population groups, has not been reported in patients with different degrees of kidney insufficiency.

MATERIALS AND METHODS

Study group

Patients admitted to the Medical Ward in TIRUNELVELI MEDICAL COLLEGE HOSPITAL with chronic renal failure who are on conservative management.

Study design

Single Centre, Cross-sectional study

Study period

Study was conducted between **September 2009- September 2010** for a period of 12 months.

Sample size

In the study period of 12 months, among patients admitted in Medical Ward after applying inclusion and exclusion criteria, 50 patients were included in this study. Patients who fulfill the criteria for CRF and who are on conservative management were taken for the study. Thyroid profile is done in all patients who fulfill the criteria.

Informed consent was Obtained from all patients

Inclusion Criteria for Chronic Renal Failure

1. Symptoms of uremia for 3 months or more.
2. Elevated blood urea, serum creatinine and decreased creatinine clearance.

3. Ultra sound evidence of chronic renal failure:
    a) Bilateral contracted kidneys – size less than 8 cm in male and female.
    b) Poor corticomedullary differentiation.
4. Supportive laboratory evidence of CRF like anemia, low specific gravity, changes in serum electrolytes, etc.,
5. Radiological evidence of renal osteodystrophy.

Exclusion criteria

1. Patients underwent peritoneal dialysis or hemodialysis.
2. Nephrotic range of proteinuria.
3. Low serum protein especially albumin.
4. Other conditions like:
    a. Acute illness
    b. Recent surgery, trauma or burns
    c. Diabetes mellitus
    d. Liver diseases
    e. Drugs altering thyroid profile like amiodarone, steroids, dopamine, phenytoin, beta-blocker, estrogen pills and iodine-containing drugs.

Detailed clinical history and examination is undertaken with preference to thyroid and renal diseases.

The following investigations are performed:

* Urine for specific gravity and broad cast
* Renal parameters like blood urea, serum Creatinine and creatinine clearance (using Modified diet and renal disease)
* Serum calcium
* Serum cholesterol for hypothyroidism
* 24 hours urine protein and serum protein to rule out nephrotic syndrome and hypoproteinemia respectively
* ECG and chest X ray to look for features for hypothyroidism and renal failure like pleural effusion, pericardial effusion
* X ray wrist, forearm and spine for evidence of renal osteodystrophy
* USG abdomen for evidence of chronic renal failure.

After selecting the patients, fulfilling the above criteria, about 5 ml of blood sample is collected in non-heparinised serum bottle and sent for thyroid profile.

Components of thyroid profile in this study

* Serum triiodothyronine(T3)-70-200 ng/dl.
* Serum thyroxine(T4)-4.5-12.5 µg/dl.
* Serum free T3-1.4-4.0 pg/ml.
* Serum free T4-0.80-2.0 ng/dl.
* Serum thyroid stimulating hormone(TSH)-0.3-5.0µI U/ml.

OBSERVATIONS AND RESULTS

50 patients with chronic kidney disease who were on conservative management were studied. Among 50 patients, 13 patients were female and 37 patients were male.

The duration of CRF in this study varied from 3 months to 1 year. The creatinine clearance varied from 3ml/min to 64ml/min. 29 patients had creatinine clearance of <15ml/min accounting for 58%, 16 patients had creatinine clearance of 15ml – 29ml / min accounting for 32%, 5 patients had creatinine clearance of ≥30ml/min accounting for 10%.

24hrs urine protein excretion was <1gm/day in all patients in this study group. Serum calcium was normal in all patients. 70% of the patients had anemia with peripheral smear revealing normocytic normochromic anemia in 50% and hypochromic anemia in 20% of the patients. 4 patients in this study had pleural effusion, 1 patient showed evidence of osteodystrophy.

STATISTICAL ANALYSIS

The prevalence of thyroid dysfunction in chronic kidney disease trial was described and analyzed in terms of percentages and averages. The analytical data was interpreted by students unpaired and students proportion‘t’ test. The relations between the related biochemical variable in CKD were analyzed and interpreted by the point biserial correlation coefficient (r_{p1bis}). The correlation between the thyroid indices were analyzed and interpreted by the Karl Pearson’s coefficient(r). The above analysis and interpretation of statistical procedures were performed by the statistical package S.P.S.S.(13). The value of $P < 0.05$ was considered as significant.

RESULTS

The clinical trial was described and analyzed according to their age, sex and prevalence of thyroid dysfunction.

TABLE 1: SEX WISE AGE DISTRIBUTION OF PATIENTS TAKEN FOR STUDY

Age group in years	Male		Female		Total	
	frequency	%	frequency	%	frequency	%
30-39	8	21.6	0	Nil	8	16
40-49	4	10.8	5	38.4	9	18
50-59	10	27	6	46.2	16	32
60-69	15	40.5	2	15.4	17	34
total	37	100	13	100	50	100
Median age	55(35-69)		55(40-62)		55(35-69)	
mean±S.D.	53.8±11.8		51.5±7.2		52.7±10.3	
't'	0.486					
Significance	d.f.=48 P>0.05					

The sex wise age distribution shown in the table 1 reveals that the median age of the males and females and total clinical trials was 55 years. The mean age of the total subjects was 52.7±10.3 years. The mean age of the

male and female patients was 53.8±11.8 and 51.5±7.2 years respectively. The difference between the mean age of the male and female was statistically not significant P>0.05. The male participation was 74% and the female participation was 26%.

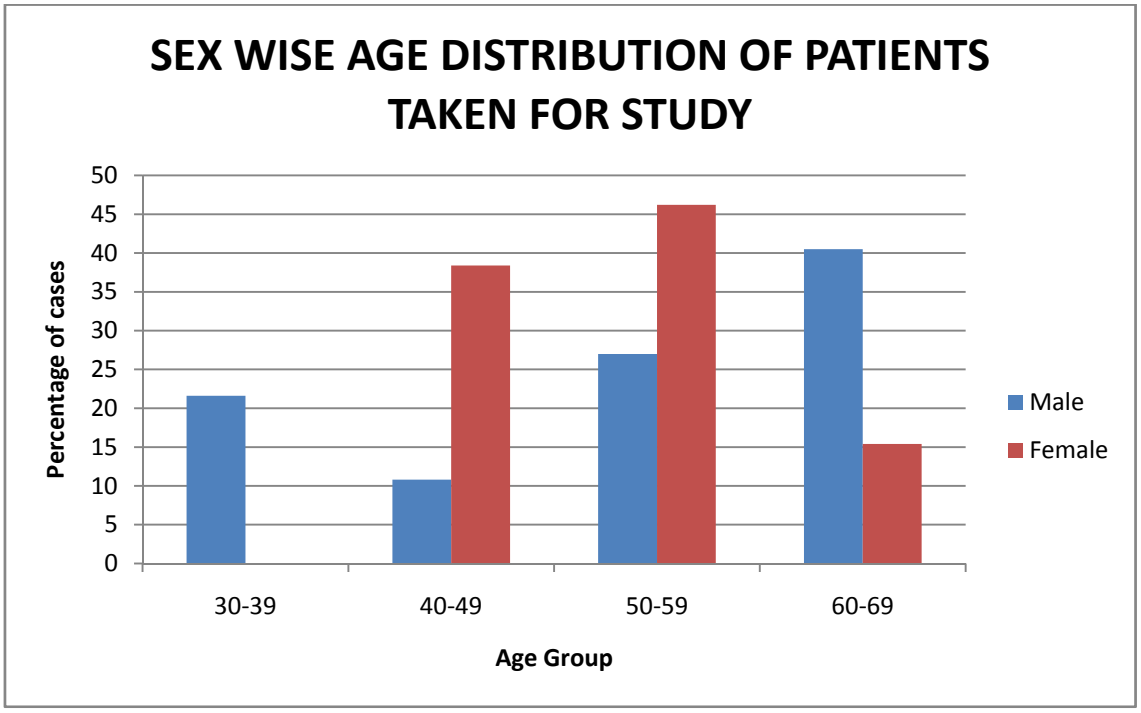
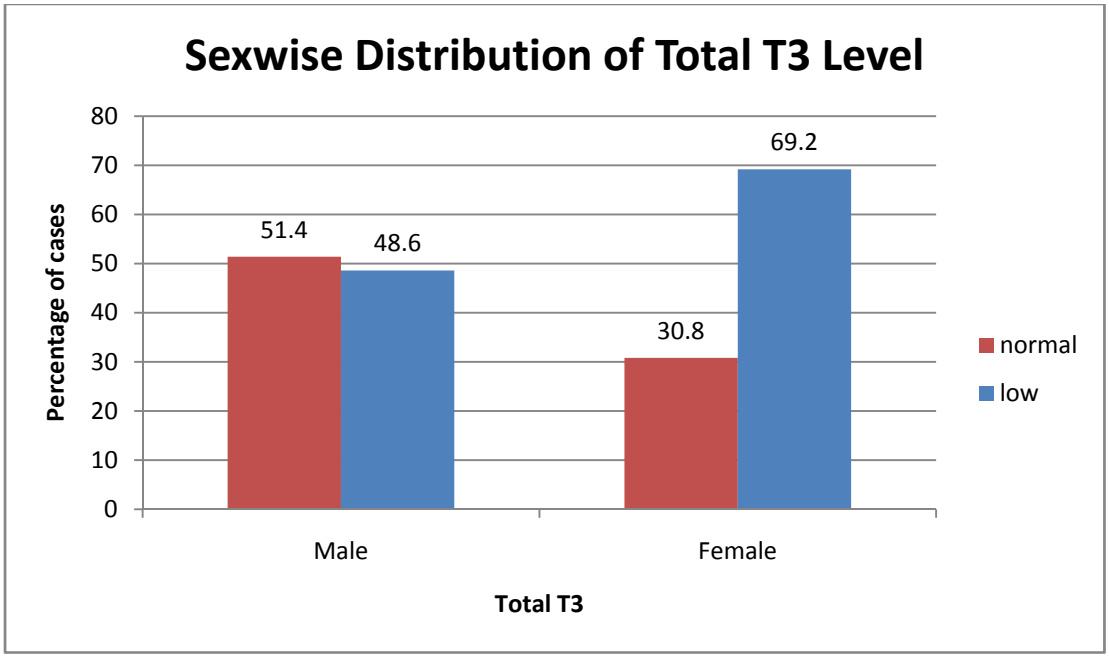


TABLE 2 : SEX WISE PREVALANCE OF THYROID DYSFUNCTION IN CKD PATIENTS

Thyroid hormones	Level of hormone	No	Males, n=37		Females=13		't'	Significance
			frequency	%	frequency	%		
T3	low	27	18	48.6	9	69.2	1.354	P>0.05
	normal	23	19	51.4	4	30.8		
T4	low	11	7	18.9	4	30.8	0.830	P>0.05
	normal	39	30	81.1	9	69.2		
TSH	high	2	1	2.7	1	7.7	0.636	P>0.05
	normal	48	36	97.3	12	92.3		

The prevalence of thyroid dysfunction among the sexes was shown in the above table 2. The prevalence of low T3 syndrome was 54% (27 cases) and the low T4 syndrome was 22 % (11 cases). The prevalence of TSH in hypothyroidism range was 4 %(2 cases). Among the males 48.6% of patients had low T3 syndrome. And among the females was 62.2%. The difference was not statistically significant P>0.05. The prevalence of low T4 among the males was 18.9 % and among the females was 30.8%. The difference among the sexes was not statistically significant i.e. P>0.05. The prevalence of TSH in clinical hypothyroidism range among males was 2.7%. And among the females was 7.7%. The prevalence between the sexes was not statistically significant (P>0.05).


Sexwise Distribution of Total T3 Level
Percentage of cases
80
70
60
50
40
30
20
10
0
51.4
48.6
30.8
69.2
Male
Female
Total T3
normal
low

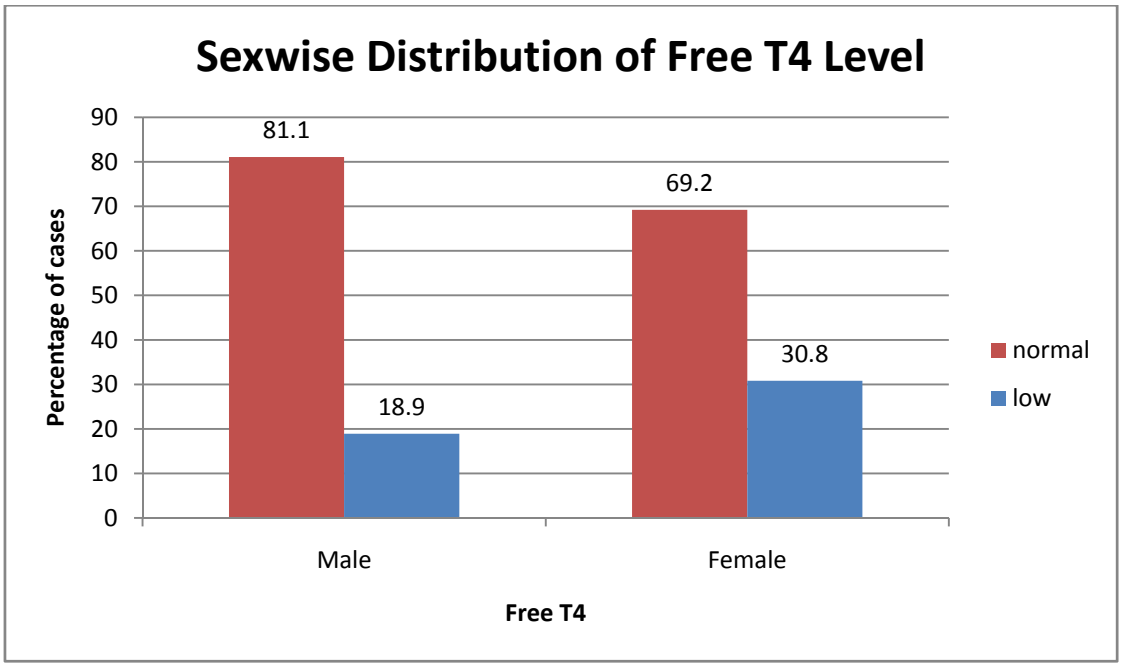

Sexwise Distribution of Free T4 Level
Percentage of cases
90
80
70
60
50
40
30
20
10
0
81.1
18.9
69.2
30.8
Male
Female
Free T4
normal
low

TABLE 3: AGE WISE THYROID HORMONES AND TSH DISTRIBUTION TAKEN FOR STUDY

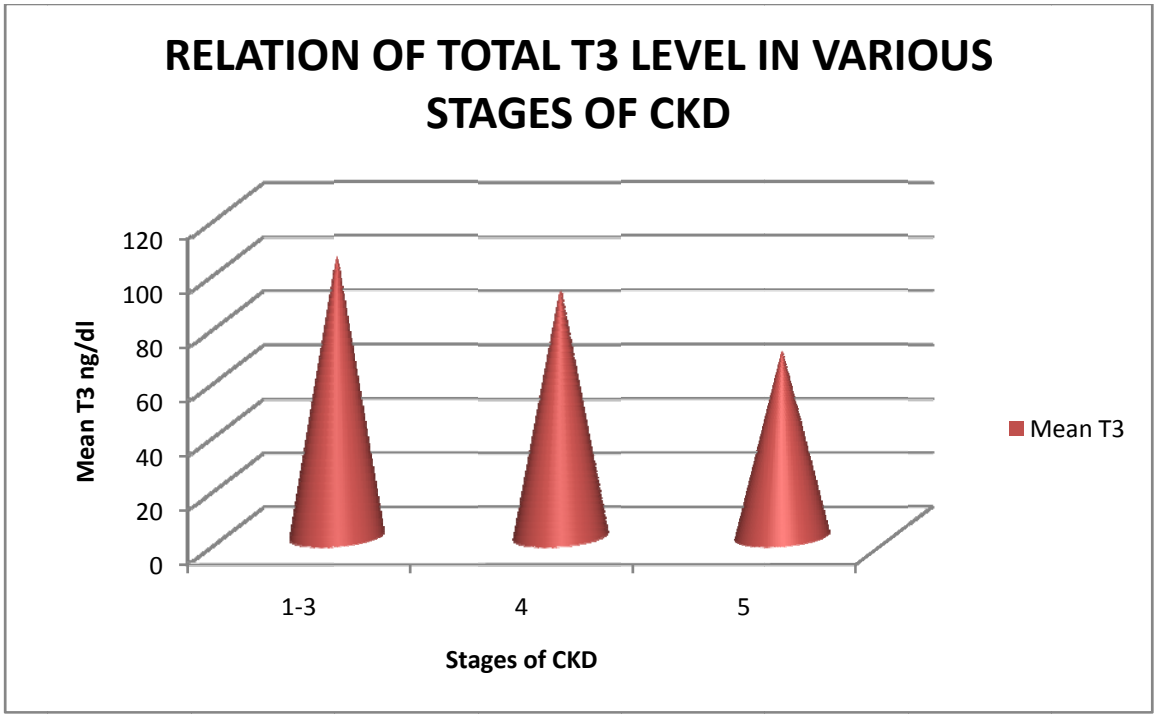
Age group	Frequency	Mean Total T3	Mean Free T4	Mean TSH
30-39	8	75.8±23.8	0.8±0.2	11±25.9
40-49	9	70.4±33.5	0.9±0.2	3±3.2
50-59	16	71.4±26.3	1.1±0.2	1.3±1.2
60-69	17	95.3±33.6	1.1±0.3	1.3±1
Total	50	80±31.1	1±0.3	3.2±10.5

The above table 3 reveals that the mean level of thyroid biomarkers does not show significant difference in the various age groups.

TABLE 4: DISTRIBUTION OF TOTAL T3 FREE T4 AND TSH IN VARIOUS STAGES OF CKD

Stages of CKD	Frequency	Mean Total T3	Mean free T4	Mean TSH
1-3	5	103.4±30.7	1.25±0.1	1.8±1.9
4	16	91±36.6	1.1±0.2	1.2±0.8
5	29	68.8±24	0.9±0.3	4.5±13.7

The above table 4 reveals the mean T3, free T4 and TSH levels in various stages of CKD. The mean T3 is decreased significantly with reduced creatinine clearance. The free T4 is also significantly decreased in stage 5 CKD.


RELATION OF TOTAL T3 LEVEL IN VARIOUS STAGES OF CKD
Mean T3 ng/dl
120
100
80
60
40
20
0
1-3
4
5
Stages of CKD
Mean T3

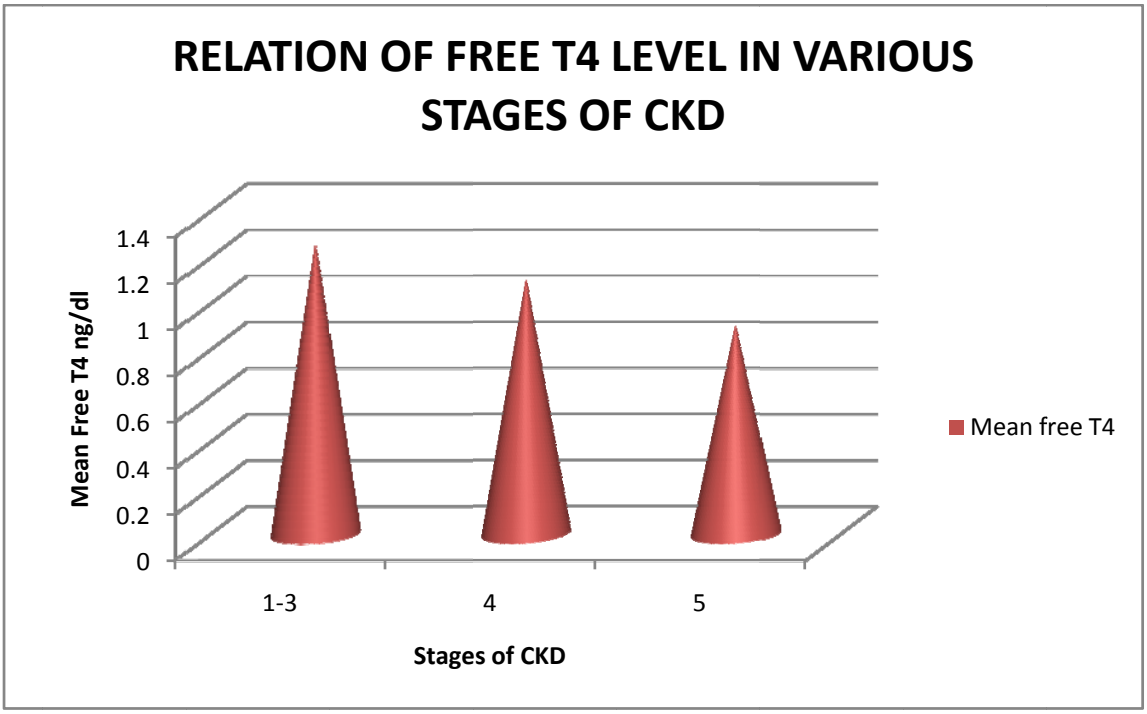
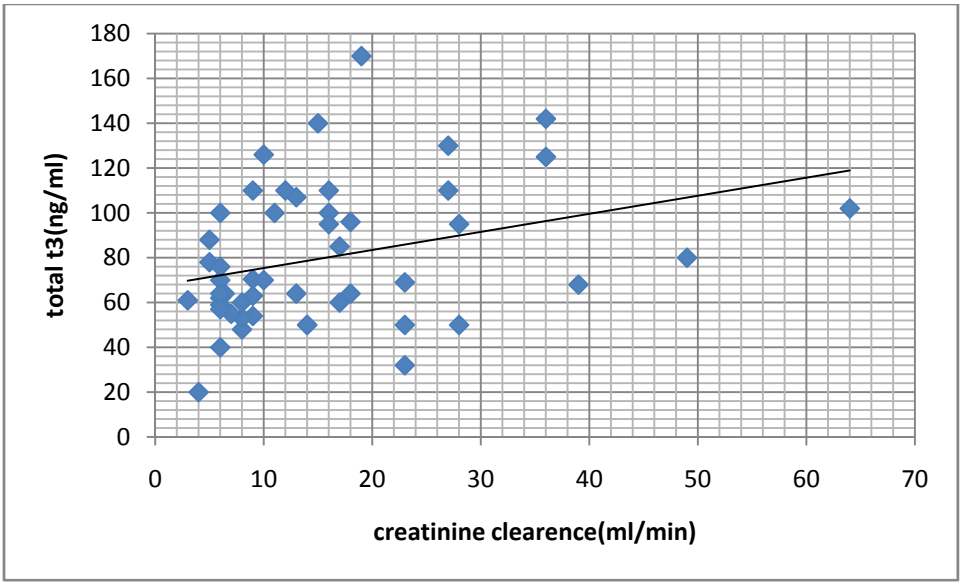

RELATION OF FREE T4 LEVEL IN VARIOUS STAGES OF CKD
Mean Free T4 ng/dl
1.4
1.2
1
0.8
0.6
0.4
0.2
0
1-3
4
5
Stages of CKD
Mean free T4

TABLE 5 : RELATIONSHIP BETWEEN CREATININE CLEARANCE WITH TOTAL T3, FREE T4 AND TSH

Relation with Cr. Clearance	r	Significance
Total T3	0.320	P<0.05
Free T4	0.381	P<0.01
TSH	-0.133	P>0.05

The above table shows positive correlation between total T3 and Creatinine clearance and it is statistically significant. The free T4 and creatinine clearance shows positive correlation and it is statistically significant. The above table shows negative correlation of TSH with creatinine clearance and it is not statistically significant.

CORRELATION OF TOTAL T3 WITH CREATININE CLEARANCE



CORRELATION OF FREE T4 WITH CREATININE CLEARANCE

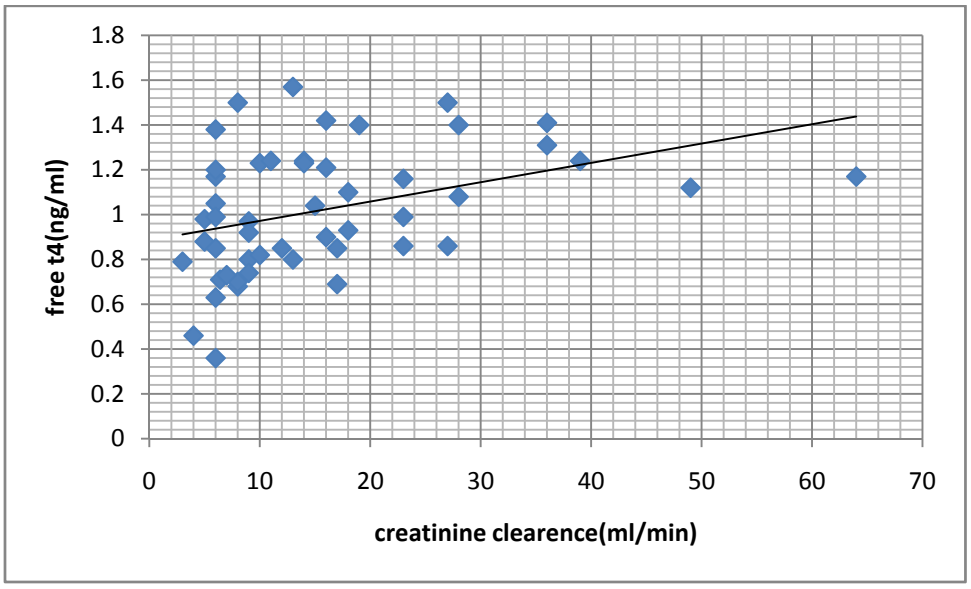


TABLE 6: CORRELATION OF TOTAL T3 WITH CREATININE CLEARANCE

Creatinine clearance ml/min	T3 dysfunction		Normal		Total		r_{p1bis}	d.f.	Significance
	No.	%	No.	%	No.	%			
60-89	0	0	1	4.3	1	2			
30-59	1	3.7	3	13	4	8			
15-29	6	22.2	10	43.5	16	32			
<15	20	74.1	9	39.1	29	58	-	48	P<0.05
total	27	100	23	100	50	100	0.316		
Mean±S.D	12.2±8.6		20±14.8		15.8±12.3				
't'	2.338								
Significance	P<0.05								

The table 6 explains the relation between the creatinine clearance with total T3. The mean creatinine clearance in low T3 syndrome was 12.2±8.6 ml and in normal patients was 20±14.8 ml. The difference between the patients was statistically significant i.e. P<0.05. The r_{p1bis} determines the direction between the creatinine clearance with low total T3 patients. The dysfunction with creatinine clearance was negatively correlated i.e. r_{p1bis} = -0.316. Statistically explain the negative relationship between them significantly i.e. P<0.05.

TABLE 7 : RELATIONSHIP BETWEEN CREATININE CLEARANCE WITH FREE T4

Creatinine clearance ml/min	FREE T4 dysfunction		Normal		Total		r_{p1bis}	d.f.	Significance
	No.	%	No.	%	No.	%			
60-89	0	0	1	2.6	1	2	-0.340	48	P<0.05
30-59	0	0	4	10.3	4	8			
15-29	1	9.71	15	38.5	16	32			
<15	10	90.4	19	48.6	29	58			
Total	11	100	39	100	50	100			
Mean±S.D	7.9±4		18±13		15.8±12.3				
't'	2.518								
Significance	P<0.05								

The table 7 describes the correlation between the creatinine clearance with free T4. The mean creatinine clearance with low free T4 dysfunction and normal patients was 7.9±4 and 18±3 ml respectively. The difference between the mean was statistically significant i.e. P<0.05. The point biserial correlation coefficient i.e. r_{p1bis} = -0.340 illustrated the negative correlation.

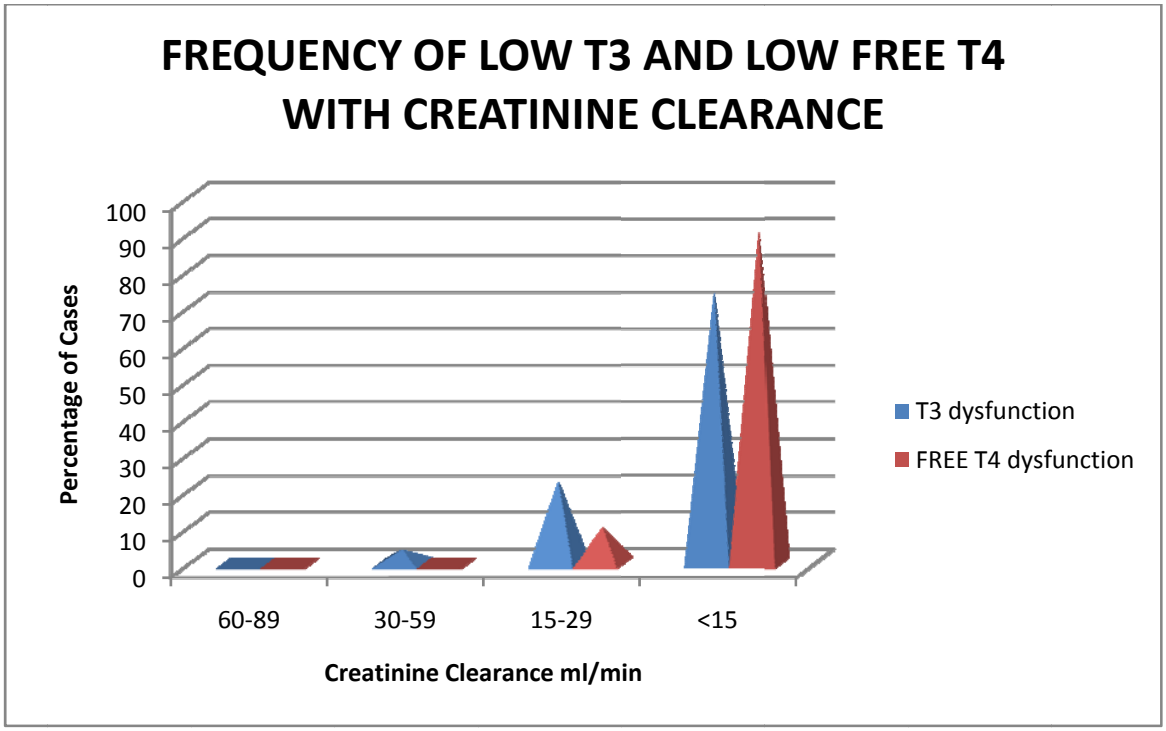


TABLE 8: RELATIONSHIP BETWEEN CREATININE CLEARANCE WITH TSH

Creatinine clearance ml/min	High TSH		Normal		Total		r_{p1bis}	d.f.	Significance
	No.	%	No.	%	No.	%			
60-89	0	0	1	2.1	1	2.1	-0.178	48	P>0.05
30-59	0	0	4	8.3	4	8			
15-29	0	0	16	33.3	16	32			
<15	2	100	27	56.3	29	58			
total	2	100	48	100	50	100			
Mean±S.D	5±1.4		16.2±12.4		15.8±12.3				
't'	1.271								
Significance	P>0.05								

The relationship displayed in the table 8 reveals the mean creatinine clearance in TSH dysfunction and normal were 5±1.4 and 16.2±12.4 ml respectively. The difference between the mean was not statistically significant i.e.P>0.05.

TABLE 9: PREVALANCE OF GOITER IN CHRONIC KIDNEY DISEASE PATIENTS

S.No.	Disease	No.	%
1	Goiter	2	4
2	Goiter with pleural effusion	1	2
3	No evidence	47	94

The above table 9 describes the prevalence of goiter in CKD patients. Among the 50 patients 47(94%) patients had no evidence of goiter. With remaining 3patients 2(4%) patients had exclusively goiter , 1 (2%)patients had goiter with pleural effusion . The total prevalence of goiter in our study is 6%.

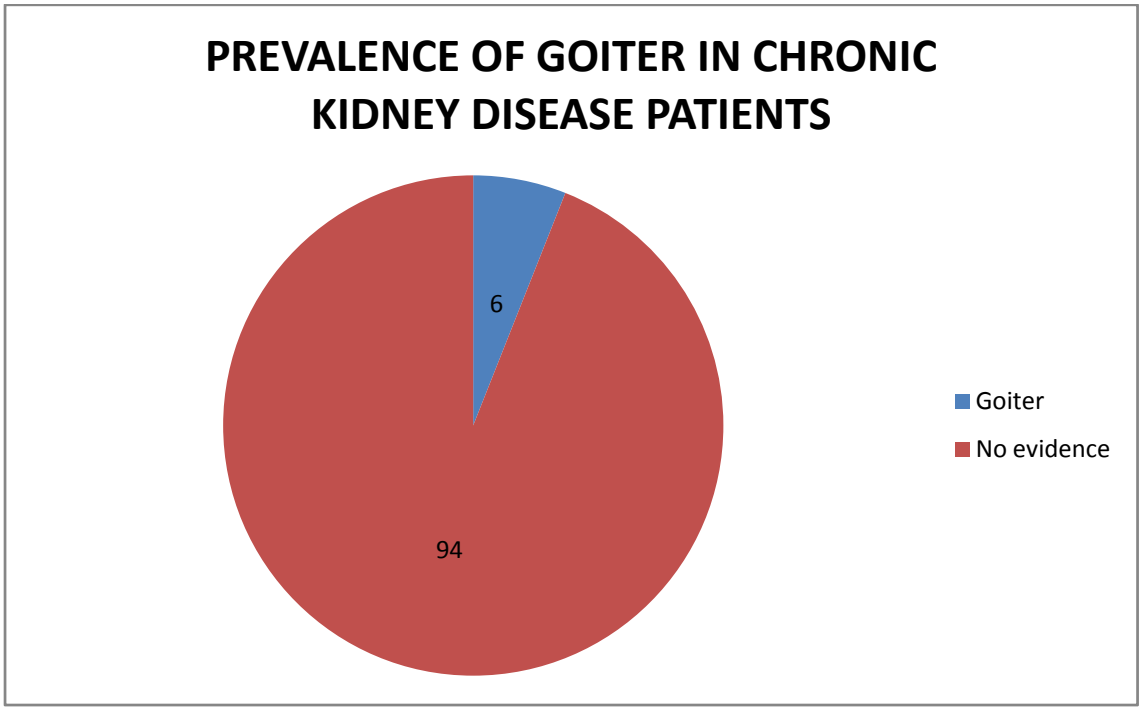
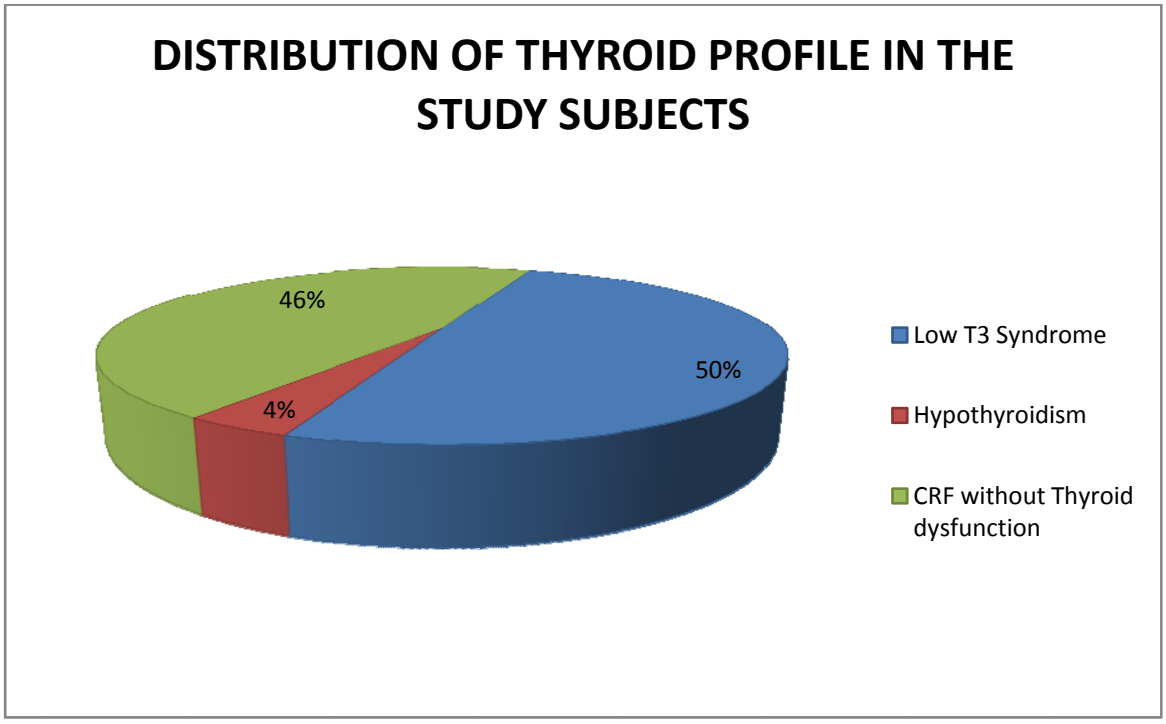

PREVALENCE OF GOITER IN CHRONIC KIDNEY DISEASE PATIENTS
6
94
Goiter
No evidence

Table-10 : RELATIONSHIP BETWEEN TOTAL T3 WITH TSH EXCLUDING HYPOTHYROIDISM

S.NO.	LOW T3 (ng/dl)	TSH (µIU/ml)
1	64	2.55
2	61	3.06
3	60	0.40
4	64	0.97
5	70.4	0.87
6	62	0.49
7	48	0.49
8	69	0.96
9	54	0.46
10	53	1.61
11	70	4.35
12	59	2.13
13	64	2.71
14	55	4.85
15	50	1.52
16	50	1.80
17	64	0.64
18	50	1.20
19	50	0.74
20	57	2.12
21	63	1.01
22	60	3.17
23	70	0.30
24	68	0.99
25	32	0.50

This table shows relationship between low T3 and TSH excluding hypothyroidism. The mean value of TSH in low T3 syndrome is 1.6±1.2. According to our study, in patients with low T3 syndrome the mean value of TSH in various stages of renal failure are within normal range.



DISCUSSION

A large number of hormonal systems are affected by CRF, yet it remains unclear to what extent these changes are responsible for manifestations of uremic syndrome. Patients with CRF often have signs & symptoms suggestive of thyroid dysfunction & hence the diagnosis of thyroid disease in these patients has obvious prognostic implications. The data reported deals primarily with the biochemical parameters. In uremia the mean values of both serum T3 & T4 were significantly low. This is comparable to **Ramiraz et al.[3] and Lim VS et al.[17]**study. In our study, out of 50 patients 27 patients (54%) had low T3 syndrome. The prevalence of low T3 in stage 1- 3 is 20 %, for stage 4 is 38%, and stage 5 is 70%. This observation is consistent with **Sang Heon Song et al.[4]** in which the prevalence of low T3 will be increased according to the increase in stage of CKD. In our study there is a positive correlation between Total T3 and creatinine clearance and it is statistically significant $P<0.05$.This shows serum T3 levels were associated with severity of CKD even in the normal TSH level.

There was higher frequency of reduced free T4 values in our study (22%) which is consistent with **Kaptein et al.[5] and Avasthi et al.[6]** study but it is not statistically significant. In our study there is a positive correlation between Free T4 and creatinine clearance and it is statistically significant $P<0.05$. Out of the 50 uremic patients 2 patients show TSH >10 μIU/ml.

The high serum TSH level is > 75 μIU/ml. Both these patients had very low serum T3 concentration which can be explained by the normal feedback regulation of the pituitary thyroid axis. One patient is having both goiter and pleural effusion. This observation is consistent with **Joseph et al.**[50] who studied 175 patients of CRF who had low T3, T4, fT4 but had high TSH levels suggested maintenance of pituitary thyroid axis. 48 patients i.e. 96% reported normal level of serum TSH ≤5 μIU/ml. Out of 48 patients 25 patients had low T3 and 9 patients had low total T3 and free T4. So these 25 patients had normal level of serum TSH in spite of low serum T3 level. They demonstrated abnormality in the hypophyseal mechanism of TSH release in uremic patients as the TSH response to TRH was blunted. These results are consistent with study of **Spector et al.**[49] and **Ramirez et al.** reported normal level of serum TSH in patients of CRF in spite of low serum T3 levels.

In **Mehta H.J. Joseph et al.**[7] study low TT3, FT3 and TT4 values is seen in clinically euthyroid CKD patients. However finding of normal T4 values and TSH would indicate functional euthyroid status. It can be presumed that free T4 values would fall if these patients develop hypothyroidism and TSH values would rise simultaneously. Thus Free T4 and TSH levels combined can be used for the diagnosis of hypothyroidism in presence of CKD.

Subjects with TSH > 10 μIU/ml and free T4 below the reference range have overt primary hypothyroidism and should be treated with thyroid hormone replacement.

The prevalence of primary hypothyroidism in CKD ranges from 0-9.5% as evidenced in previous studies. The prevalence of hypothyroidism in our study is 4%. This is consistent with results of **Kaptein et al.**[5]

Ramirez et al.[3] reported high prevalence of goiter in CRF patients especially those on chronic dialysis. Incidences were increased in end stage renal disease. The possible explanation is due to accumulation of iodides in thyroid gland due to decreased renal clearance in CRF patients. Study conducted by **Hegedus et al.**[8] showed thyroid gland volume was significantly increased in patients with CRF.

In our study, 3(6%) patients had evidence of goiter. Out of 3 patients, 1(2%) had clinical and biochemical features of hypothyroidism. Remaining 2 patients had low T3 level with normal TSH and T4.

Dialysis

As stated previously, Hemodialysis and continuous ambulatory peritoneal dialysis have shown to affect the thyroid profile independently of CRF. Also drugs like heparin, furosemide used during dialysis will affect the thyroid profile.

Kayima et al.[9] and **Giordano et al.**[10] have conducted studies regarding effect of dialysis on CRF patients with thyroid dysfunction.

This study showed no significant improvement in thyroid profile after repeated hemodialysis.

But in the patients who have undergone renal transplant surgery,most of the thyroid function parameters returned to normal with TSH below normal.

CONCLUSION

1. The prevalence of thyroid dysfunction in patients with CKD is 54%.
2. Number of patients with low T3 and T4 syndrome progressively increases with severity of renal failure.
3. Serum level of total T3 and free T4 is directly proportional to creatinine clearance level.
4. Total T3 and free T4 had correlation with the severity of renal failure.
5. TSH values will be useful to differentiate hypothyroidism from non-thyroidal illness due to CKD.
6. Only 6% of the study population had evidence of goiter.
7. Alteration in the values of T3 and T4 occurs as a part of body adaptation mechanism to conserve energy.

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PROFORMA

Name: Age: Sex:

IPNo: Occupation:

Address:

Past H/O:

HT: Y/N,

DM: Y/N,

Recent surgery/Trauma: Y/N ,

Drugs: Y/N

Jaundice: Y/N

Other systemic illness: Y/N

Menstrual and Obstetric History:

General Exam:

1. Nourishment:
2. Pallor:
3. Facial puffiness:
4. Pedal edema:
5. Skin texture:
6. Thyroid swelling:

Pulse:

BP:

Respiratory rate:

Temperature:

CVS:

RS :

Abdomen :

CNS :

Investigations:

1. Urine complete examination:
2. Blood:
    - Hb: gm/dl
    - TC:
    - DC: P %L %E %
    - RBC: Cells/cumm
    - BT: mnte
    - CT: mnte
    - Peripheral smear
3. Blood
    - Urea:
    - Creatinine:
    - Na^{+}:
    - K^{+}:
    - Ca^{2+}:
    - Serum Cholesterol
    - Serum protein Total
        - Albumin
        - Globulin
4. ECG
5. X-rays
    - Chest X-ray
    - X-ray wrist, forearm, vertebral spine
6. USG abdomen
7. 24 hrs urine protein

8. Thyroid profile

Serum triiodothyroine

Serum thyroxin

Serum free T3 and serum free T4

Serum thyroid stimulating hormone

MASTER CHART

S.NO	IP. No.	Age	Sex	Symptoms Duration (months)	Renal Parameters			Thyroid Profile					Miscellaneous
					Blood Urea (mg/dl)	Sr. Creatinine (mg/dl)	Cr. Clearance (ml/min)	Total T3 (ng/dl)	Total T4 (µg/dl)	Free T3 (pg/ml)	Free T4 (ng/dl)	TSH (µIU/ml)	NIL
1	43736	63	M	4	185	9.0	6.41	64	4.43	1.16	0.71	2.55	NIL
2	43926	66	M	6	92	3.8	17	85	4.84	1.5	0.85	1.42	NIL
3	43846	35	M	5	85	4.0	18	96	5.66	1.82	0.93	0.55	3
4	43976	35	M	4	117	10.0	6	40	1.6	0.91	0.36	75	NIL
5	44016	40	F	9	243	13.2	3	61	3.93	1.22	0.79	3.06	NIL
6	44975	60	M	11	58	2.0	36	125	7.43	2.03	1.31	1.09	NIL
7	44955	52	M	5	68	4.0	17	60	3.92	1.11	0.69	0.4	NIL
8	44226	40	F	10	108	4.1	13	64	4.43	1.09	0.8	0.97	NIL
9	43978	35	M	8	110	2.8	28	95	6.54	1.9	1.08	3.21	NIL
10	42736	65	M	6	80	3.2	13	107	6.24	1.93	1.57	0.73	NIL
11	43928	67	M	6	190	6.4	9	70.4	4.64	1.39	0.8	0.87	NIL
12	41972	67	M	12	55	1.2	64	102	6.36	1.65	1.17	1.12	NIL
13	44343	60	M	5	153	10.0	6	62	5.32	1.34	1.17	0.49	NIL
14	44296	55	F	6	75	2.3	23	32	6.62	1.32	0.99	0.5	3
15	44978	56	M	8	216	12.0	5	78	4.79	1.45	0.88	0.57	2
16	45570	51	M	6	112	8.0	8	48	3.8	1.07	0.68	0.49	NIL
17	45069	50	M	7	117	6.5	10	126	7.5	2.24	1.23	0.5	NIL
18	44207	37	M	4	84	3.2	23	69	5.78	1.32	0.86	0.96	NIL
19	44396	46	M	8	142	6.8	9	54	4.82	1.18	0.97	0.46	NIL
20	44121	36	M	3	192	7.8	8	53	3.6	1.16	0.7	1.61	NIL
21	45213	69	M	10	113	8.7	6	70	4.59	1.39	1.2	4.35	1
22	47161	55	F	10	120	7.5	6	59	5.5	1.2	1.05	2.13	2
23	45577	56	M	7	245	10.6	5	88	5.06	1.65	0.98	5	NIL
24	46871	38	M	4	96	7.1	9	110	4.62	2.7	0.92	0.57	NIL
25	46972	42	M	5	137	4.0	18	64	5.72	1.21	1.1	2.71	NIL
26	45166	45	F	6	198	7.0	7	55	3.57	1.1	0.73	4.85	NIL
27	45913	50	M	9	109	4.1	16	100	7.59	2.62	1.42	1.11	NIL
28	46945	50	M	5	121	4.6	14	50	4.85	1.04	1.24	1.52	NIL
29	46420	65	M	11	123	4.4	14	50	5.62	1.07	1.23	1.8	NIL
30	46355	55	M	4	160	5.8	11	100	4.85	2.63	1.24	1.82	3

31	46783	55	F	4	128	7.6	6	64	7.02	1.3	1.38	0.64	NIL
32	45730	36	M	3	85	1.7	49	80	5.54	1.84	1.12	5.27	NIL
33	44185	46	M	7	158	10.0	6	100	4.61	2.36	0.85	0.55	NIL
34	41078	63	M	12	89	4.0	16	110	4.54	2.84	0.9	0.72	NIL
35	28861	57	M	11	77	3.0	23	50	6.39	1.24	1.16	1.2	NIL
36	32906	62	F	12	55	2.0	27	110	5.78	1.94	0.86	0.94	NIL
37	41726	65	M	4	87	3.5	19	170	7.2	2.8	1.4	0.54	NIL
38	42803	60	F	5	42	2.0	27	130	8.2	2.7	1.5	1.73	NIL
39	40408	55	F	7	53	2.0	28	50	7.7	1.1	1.4	0.74	NIL
40	48531	60	M	8	45	2.0	36	142	8.56	2.65	1.41	0.77	2,3
41	48518	60	M	8	204	10.0	6	57	3.04	0.99	0.63	2.12	NIL
42	48149	65	M	9	140	4.0	16	95	6.8	2.11	1.21	1.32	NIL
43	45956	45	F	6	93	3.6	15	140	5.5	2.8	1.04	0.55	NIL
44	46871	38	M	4	96	7.1	9	63	4.08	1.26	0.74	1.01	NIL
45	49009	48	M	3	161	10.0	6	76	5.56	1.72	0.99	2.91	NIL
46	31487	55	F	7	106	5.8	8	60	8.34	1.26	1.5	3.17	NIL
47	38721	55	F	11	69	4.0	12	110	4.72	2.62	0.85	0.62	1
48	48912	65	M	7	175	5.9	10	70	4.59	1.36	0.82	0.3	NIL
49	49044	55	M	12	29	1.9	39	68	7.16	1.32	1.24	0.99	1,2
50	45854	47	F	4	220	12.0	4	20	1.31	0.84	0.46	10.6	1,2

Key to Master Chart

Cr Cl Creatinine Clearance
1 Goiter
2 Pleural effusion
3 Papilloedema
M Male
F Female